

wherein,

Sub B1
R¹ is a heterocyclic ring substituted with (a) four C1-4 alkyl or (b) one substituent selected from the following (i)-(xii), and the said ring may be substituted with 1 to 3 of substituent(s) selected from the group consisting of (i)-(xxiii):

(i) oxo,

(ii) C5-8 alkyl,

(iii) -COO-R⁵ (in which, R⁵ is hydrogen, C5-8 alkyl, C2-8 alkenyl, or C1-4 alkyl substituted with 1 to 3 of halogen or C1-4 alkoxy),

(iv) -(C1-4 alkylene)-COOR⁶ (in which, R⁶ is hydrogen, C1-8 alkyl, C2-8 alkenyl or C1-4 alkyl substituted with 1 to 3 of halogen),

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cont.
(v) -CO-R⁷ (in which, R⁷ is C5-8 alkyl, C2-4 alkenyl, carbocyclic ring, heterocyclic ring or C1-8 alkyl substituted with one substituent selected from the following (1)-(8):

(1) carbocyclic ring,

(2) heterocyclic ring,

(3) hydroxy,

(4) C1-4 alkoxy,

(5) -OCO-(C1-4 alkyl),


(6) -O-(C1-4 alkylene)-O-(C1-4 alkyl),

(7) NR⁸R⁹ (in which, R⁸ and R⁹ each, independently, is hydrogen or C1-4 alkyl),

(8) halogen),

(vi) -(C1-4 alkylene)-CO-R¹⁰ (in which, R¹⁰ is C1-8 alkyl, C2-4 alkenyl, carbocyclic ring, heterocyclic ring or C1-8 alkyl substituted with one substituent selected from the following (1)-


(8):

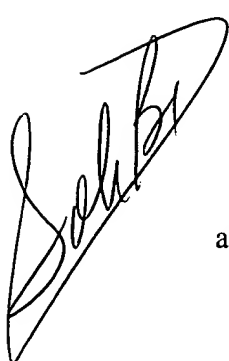
- 
- (1) carbocyclic ring,
 - (2) heterocyclic ring,
 - (3) hydroxy,
 - (4) C1-4 alkoxy,
 - (5) -OCO-(C1-4 alkyl),
 - (6) -O-(C1-4 alkylene)-O-(C1-4 alkyl),
 - (7) NR¹¹R¹² (in which, R¹¹ and R¹² each, independently, is hydrogen or C1-4 alkyl),
 - (8) halogen),

(vii) -CO-CO-R¹³,


(viii) -CO-(C1-4 alkylene)-CO-R¹⁴,

(ix) -SO₂-R¹⁵ (in which, R¹³, R¹⁴ and R¹⁵ each, independently, is C1-8 alkyl, C2-4 alkenyl, carbocyclic ring, heterocyclic ring, hydroxy, C1-4 alkoxy or C1-8 alkyl substituted with one substituent selected from the following (1)-(8):

- 
- (1) carbocyclic ring,
 - (2) heterocyclic ring,
 - (3) hydroxy,
 - (4) C1-4 alkoxy,

- 
- (5) -OCO-(C1-4 alkyl),
(6) -O-(C1-4 alkylene)-O-(C1-4 alkyl),
(7) $\text{NR}^{16}\text{R}^{17}$ (in which, R^{16} and R^{17} each, independently, is hydrogen or C1-4 alkyl),
(8) halogen),
(x) -CONR¹⁸R¹⁹ (in which, R^{18} is hydrogen or C1-4 alkyl which may be substituted with one phenyl, R^{19} is C1-8 alkyl or C2-4 alkenyl),
(xi) C1-8 alkyl substituted with 1 to 2 of substituent(s) selected from the group consisting

of the following (1)-(7):

- 
- (1) hydroxy,
(2) C1-4 alkoxy,
(3) -O-(C1-4 alkylene)-O-(C1-4 alkyl),
(4) tetrahydropyran-2-yloxy,
(5) -SR²⁰ (in which, R^{20} is hydrogen or C1-4 alkyl),
(6) halogen,
(7) $\text{NR}^{21}\text{R}^{22}$ (in which, R^{21} and R^{22} each, independently, is hydrogen or C1-4 alkyl),
(xii) hydroxy,
(xiii) C1-4 alkyl,
(xiv) C1-4 alkoxy,
(xv) phenyl,

(xvi) phenoxy,

(xvii) benzyloxy,

(xviii) $-SR^{23}$ (in which, R^{23} is hydrogen or C1-4 alkyl),

(xix) C2-5 acyl,

(xx) halogen,

(xxi) C1-4 alkoxycarbonyl,

(xxii) nitro,

(xxiii) $-NR^{24}R^{25}$ (in which, R^{24} and R^{25} each, independently, is hydrogen, C1-4 alkyl or C1-4 alkoxycarbonyl, or R^{24} and R^{25} taken together with nitrogen atom to which is attached represents 5 to 7-membered saturated heterocyclic ring necessary containing one nitrogen atom and optionally further containing one nitrogen atom or one oxygen atom),

A is single bond, $-CO-$ or $-SO_2-$,

R^2 is hydrogen or C1-4 alkyl which may be substituted with one phenyl,

D is C1-4 alkylene or C2-4 alkenylene,

E is

1) $-COO-$,


2) $-OCO-$,

3) $-CONR^{26}-$ (in which, R^{26} is hydrogen or C1-4 alkyl),


4) $-NR^{27}CO-$ (in which, R^{27} is hydrogen or C1-4 alkyl),

5) $-O-$,

6) $-S-$,

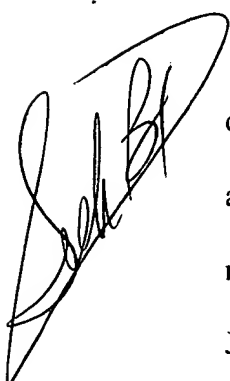
- 
- 7) -SO-,
8) -SO₂-,
9) -NR²⁸- (in which, R²⁸ is hydrogen or C1-4 alkyl),
10) -CO-,
11) -SO₂NR²⁹- (in which, R²⁹ is hydrogen or C1-4 alkyl) or
12) -NR³⁰SO₂- (in which, R³⁰ is hydrogen or C1-4 alkyl),

R³ is

- 
- 1) carbocyclic ring,
2) C1-4 alkyl substituted with carbocyclic ring,


in which, all the said carbocyclic ring and heterocyclic ring in R³ may be substituted with
1 to 3 of substituent(s) selected from the group consisting of the following (i)-(xi):

- (i) C1-4 alkyl,
(ii) C1-4 alkoxy,
(iii) phenyl,
(iv) phenoxy,
(v) benzyloxy,
(vi) -SR³¹ (in which, R³¹ is hydrogen or C1-4 alkyl),
(vii) C2-5 acyl,
(viii) halogen,
(ix) C1-4 alkoxycarbonyl,
(x) nitro,

 (xi) $-NR^{32}R^{33}$ (in which, R^{32} and R^{33} each, independently, is hydrogen, C1-4 alkyl or C1-4 alkoxy carbonyl, or R^{32} and R^{33} taken together with nitrogen atom to which is attached represents 5 to 7-membered saturated heterocyclic ring necessary containing one nitrogen atom and optionally further containing one nitrogen atom or one oxygen atom),

J is

1) -O-,

 2) $-NR^{34}-$ (in which, R^{34} is hydrogen, C1-4 alkyl which may be substituted with one phenyl, $NR^{35}R^{36}$ (in which, R^{35} and R^{36} each, independently, is hydrogen or C1-4 alkyl), hydroxy, C1-4 alkoxy, $-(C1-4 \text{ alkylene})-OH$, $-(C1-4 \text{ alkylene})-O-(C1-4 \text{ alkyl})$ or $-(C1-4 \text{ alkylene})-O-(C2-5 \text{ acyl})$),

3) $-NR^{37}-NR^{38}-$ (in which, R^{37} and R^{38} each, independently, is hydrogen or C1-4 alkyl which may be substituted with one phenyl),

4) $-NR^{39}-(C1-4 \text{ alkylene})-NR^{40}-$ (in which, R^{39} and R^{40} each, independently, is hydrogen or C1-4 alkyl which may be substituted with one phenyl),

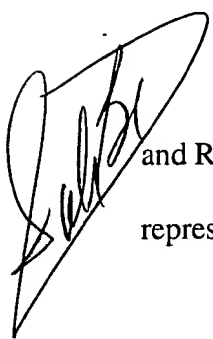
5) $-NR^{41}-(C1-4 \text{ alkylene})-O-$ (in which, R^{41} is hydrogen or C1-4 alkyl which may be substituted with one phenyl) or

6) $-NR^{42}-(C1-4 \text{ alkylene})-S-$ (in which, R^{42} is hydrogen or C1-4 alkyl which may be substituted with one phenyl),


R^4 is R^{4-1} or R^{4-2} ,

R^{4-1} is

a heterocyclic ring

 or when J is $-\text{NR}^{34}-$, $-\text{NR}^{37}-\text{NR}^{38}-$ or $-\text{NR}^{39}-(\text{C1-4 alkylene})-\text{NR}^{40}-$, each R^{4-1} and R^{34} , R^{4-1} and R^{38} , and R^{4-1} and R^{40} , taken together with the nitrogen atom to which they are attached, may represent a heterocyclic ring,

in which all the said heterocyclic ring in R^{4-1} , and heterocyclic ring represented by each R^{4-1} and R^{34} , R^{4-1} and R^{38} , and R^{4-1} and R^{40} taken together with nitrogen atom to which is attached may be substituted with 1 to 3 of substituent(s) selected from the group consisting of the following (i)-(x):

- 
- (i) C1-4 alkyl,
 - (ii) C1-4 alkoxy,
 - (iii) $-\text{SR}^{46}$ (in which, R^{46} is hydrogen or C1-4 alkyl),
 - (iv) C2-5 acyl,
 - (v) halogen,
 - (vi) C1-4 alkoxycarbonyl,
 - (vii) nitro,
 - (viii) $-\text{NR}^{47}\text{R}^{48}$ (in which, R^{47} and R^{48} each, independently, is hydrogen, C1-4 alkyl or C1-4 alkoxycarbonyl),
 - (ix) hydroxy,
 - (x) $-(\text{C1-4 alkylene})-\text{O}-(\text{C1-4 alkyl})$,
- R^{4-2} is $-\text{L}-\text{M}$,
 $-\text{L}-$ is
a -heterocyclic ring-

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or when J is -NR^{34} -, $\text{-NR}^{37}\text{-NR}^{38}$ - or $\text{-NR}^{39}\text{-(C1-4 alkylene)-NR}^{40}$ -, each L and R^{34} , L and R^{38} , and L and R^{40} , taken together with the nitrogen atom to which they are attached, may represent a heterocyclic ring,

M is

1) carbocyclic ring,
2) heterocyclic ring
3) C1-4 alkyl substituted with 1 to 2 of substituent(s) selected from the group consisting of the following (i)-(ii):

(i) carbocyclic ring,

(ii) heterocyclic ring,

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cont.
4) $\text{-O-(carbocyclic ring or heterocyclic ring)}$,
5) $\text{-S-(carbocyclic ring or heterocyclic ring)}$,
6) $\text{-NR}^{49}\text{-(carbocyclic ring or heterocyclic ring)}$ (in which, R^{49} is hydrogen or C1-4 alkyl which may be substituted with one phenyl),

7) $\text{-O-(C1-4 alkylene)-(carbocyclic ring or heterocyclic ring)}$,

8) $\text{-S-(C1-4 alkylene)-(carbocyclic ring or heterocyclic ring)}$,

9) $\text{-NR}^{50}\text{-(C1-4 alkylene)-(carbocyclic ring or heterocyclic ring)}$ (in which, R^{50} is hydrogen, C1-4 alkyl which may be substituted with one phenyl or C2-5 acyl which may be substituted with 1 to 3 of halogen) or

10) $\text{-CO-(carbocyclic ring or heterocyclic ring)}$,

See 11
or the said carbocyclic ring and heterocyclic ring in L and M, and heterocyclic ring represented by each L and R³⁴, L and R³⁸, and L and R⁴⁰ taken together with nitrogen atom to which is attached may be substituted with 1 to 3 of substituent(s) selected from the group consisting of the following (i)-(xiv):

(i) C1-4 alkyl,

(ii) C2-4 alkenyl,

(iii) hydroxy,

(iv) C1-4 alkoxy,

(v) -(C1-4 alkylene)-OH,

(vi) -(C1-4 alkylene)-O-(C1-4 alkyl),

(vii) halogen,

cont.
(viii) NR⁵¹R⁵² (in which, R⁵¹ and R⁵² each, independently, is hydrogen, C1-4 alkyl or C1-4 alkoxy carbonyl, or R⁵¹ and R⁵² taken together with nitrogen atom to which is attached represents 5 to 7-membered saturated heterocyclic ring necessary containing one nitrogen atom and optionally further containing one nitrogen atom or one oxygen atom),

(ix) SR⁵³ (in which, R⁵³ is hydrogen or C1-4 alkyl),

(x) nitro,

(xi) trifluoromethyl,

(xii) C1-4 alkoxy carbonyl,

(xiii) oxo,

(xiv) C2-5 acyl

A1
cont.

or a non-toxic salt thereof, or a hydrate thereof.

3. (Amended) A compound according to claim 1, in which E is -O- or -S-.

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4. (Amended) A compound according to claim 3, in which R³ is carbocyclic ring or C1-4 alkyl substituted with carbocyclic ring, wherein all of the carbocyclic ring may be substituted.

5. (Amended) A compound according to claim 3, in which R³ is C3-10 cycloalkyl or C1-4 alkyl substituted with C3-10 cycloalkyl, wherein all of the cycloalkyl may be substituted.

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9. (Amended) A compound according to any one of claims 3 to 5, in which R¹ is a 5 to 15-membered mono- or bi-heterocyclic ring containing 1 to 2 nitrogen atoms and 1 to 2 oxygen atoms or one sulfur atom.

10. (Amended) A compound according to claim 1 which is:

1) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-(pyridin-3-ylcarbonyl)thiazolidin-4-ylcarbonylamino)propanamide,

2) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-acetyloxymethylcarbonylthiazolidin-4-ylcarbonylamino)propanamide,

3) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-(2-methoxyacetyl)thiazolidin-4-ylcarbonylamino)propanamide,

4) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-allyloxycarbonylthiazolidin-4-ylcarbonylamino)propanamide,

5) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-(2-ethoxy-1,2-dioxoethyl)thiazolidin-4-ylcarbonylamino)propanamide,

- [Handwritten signature]*
- 6) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-((4R)-3-phenylsulfonylthiazolidin-4-ylcarbonylamino)propanamide,
- 7) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-dimethylaminomethylcarbonylthiazolidin-4-ylcarbonylamino)propanamide,
- 8) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-(morpholin-4-ylmethylcarbonyl)thiazolidin-4-ylcarbonylamino)propanamide,
- 9) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-(3-hydroxy-3-methylbutyryl)thiazolidin-4-ylcarbonylamino)propanamide,
- A3*
cont.
- 10) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-(2-hydroxyethyl)thiazolidin-4-ylcarbonylamino)propanamide,
- 11) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-(3-hydroxy-3-methylbutyl)thiazolidin-4-ylcarbonylamino)propanamide,
- 12) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-(3-hydroxypropyl)thiazolidin-4-ylcarbonylamino)propanamide,
- 13) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-carboxymethylthiazolidin-4-ylcarbonylamino)propanamide,
- 14) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-t-butoxycarbonyl-1,1-dioxothiazolidin-4-ylcarbonylamino)propanamide,
- 15) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-t-butoxycarbonyl-1-oxothiazolidin-4-ylcarbonylamino)propanamide,

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16) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-((4S)-3-t-butoxycarbonyl-2-oxooxazolidin-4-ylcarbonylamino)propanamide,

17) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-hydroxymethylcarbonylthiazolidin-4-ylcarbonylamino)propanamide,

18) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-(morpholin-4-ylcarbonylmethyl)thiazolidin-4-ylcarbonylamino)propanamide,

19) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-(2-methoxyethoxycarbonyl)thiazolidin-4-ylcarbonylamino)propanamide,

A3
cont.
20) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-chloromethoxycarbonylthiazolidin-4-ylcarbonylamino)propanamide,

21) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-(3,3-dimethylbutyryl)thiazolidin-4-ylcarbonylamino)propanamide,

22) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-cyclopentylcarbonylthiazolidin-4-ylcarbonylamino)propanamide,

23) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-2-((4R)-3-benzoylthiazolidin-4-ylcarbonylamino)propanamide,

24) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-((4R)-3-(3,3-dimethyl-1,2-dioxobutyl)thiazolidin-4-ylcarbonylamino)propanamide,

25) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-((4R)-2,2,5,5-tetramethylthiazolidin-4-ylcarbonylamino)propanamide,

A³
cont.
26) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-((2S)-1-t-butoxycarbonyl-4-oxopyrrolidin-2-ylcarbonylamino)propanamide, or

27) (2R)-N-(1-benzylpiperidin-4-yl)-3-cyclohexylmethylthio-((2S, 4R)-1-t-butoxycarbonyl-4-hydroxypyrrolidin-2-ylcarbonylamino)propanamide,
or non-toxic salts thereof.

A⁴
12. (Amended) A pharmaceutical composition comprising, as an active ingredient, an amino acid compound of the formula (I) depicted in claim 1, a non-toxic salt thereof, or a hydrate thereof.

Please add the following new claims:

A⁵
16. A method for treating or preventing, or both, a disease induced by an excessive release of neurotransmitters from N-type calcium channels, comprising administering to a host in need of such treatment an effective amount of an amino acid compound of formula (I) depicted in claim 1, a non-toxic salt thereof, or a hydrate thereof.

17. The method according to claim 16, wherein the disease induced by an excessive release of neurotransmitters from N-type calcium channels is selected from the group consisting of cerebral infarct, transient ischemic attack, encephalomyelopathy after cardiac operation, spinal angiopathy, hypertension with stress, neurosis, epilepsy, asthma and pollakiuria.

18. A method for the treatment of pain induced by an excessive release of neurotransmitters from N-type calcium channels, comprising administering to a host in need of such treatment an effective amount of an amino acid compound of formula (I) depicted in claim 1, a non-toxic salt thereof, or a hydrate thereof.